of polymorphonuclear cells (PMNs, neutrophils). Surprisingly, such PMN infiltration was almost completely absent in the C5 blocker treated mice.

During the clinical course of CIJI, an important indicator of the progression of disease is the involvement of additional limbs. Therefore, the number of limbs with clinically detectable JI at the end of the treatment period was compared with the number of limbs exhibiting JI symptoms before the start of therapy. The severity and progression of JI in each affected paw was determined and scored as described above under the heading "Materials and Methods", and the sum of the scores for all four paws of each animal was used as a "JI index". The thicknesses of all four paws of each animal were also measured with a caliper during the time of this experiment to provide a completely objective evaluation of this aspect of disease progression.

As shown in Table 1 (mean values) and Table 2 (individual values), there were significant increases in new limb involvement in the control treated group during the course of 10 day treatment, while the number of inflamed limbs was decreased when DBA/1LacJ mice with inflamed joints were treated with the C5 blocker starting at the time of disease onset. In addition to new limb recruitment, the initially affected paws of the control treated animals evidenced progression of inflammatory joint disease severity by becoming more inflamed (Figure 2a). Acute inflammation in the affected joints was observed as severe joint swelling and redness during the first few days, followed by joint deformation and ankylosis at the end of 10 day period. In contrast, no new paws were involved and the severity of inflammation in the majority of affected joints subsided or remained unchanged during the course of C5 blocker therapy (Figure 2a).

The paw thicknesses of initially affected limbs in both C5 blocker treated and control treated groups during

the course of these experiments is shown as mean values for each group in Figure 2b. Figures 3a, 3b, 3c, and 3d show values for each initially inflamed paw of each of the matched pairs of control treated and C5 blocker treated animals, while Figure 3e shows the values obtained for each initially inflamed paw of each of the unpaired C5 blocker treated animals (shown along with the mean values for control treated animals of Figure 2b). In these figures, the number in parenthesis indicates the designation of the particular animal, while the letters following the numbers (only in those cases where more than one limb was affected initially) indicate the particular paws affected, with the first letter indicating front (F) or rear (R) paws, and the second letter indicating right (R) or left (L) paws.

As can be seen in Figures 2 and 3, and in Tables 1 and 2, C5 blocker treatment successfully prevented further paw recruitment and reduced (but did not completely abolish) the inflammation in the initially affected joints in all but one (mouse #4) of the C5 blocker treated animals. As can be seen in Figure 2b, the mean thickness of initially affected paws in the control treated group increased significantly during the 10 day period, while the mean thickness of initially affected paws in the C5 blocker treated group decreased, but not significantly.

EXAMPLE 2

Prophylactic Treatment with a C5 Blocker Prevents Collagen Induced Joint Inflammation

In these experiments, the administration of the C5 blocker coincided with the reimmunization of the experimental animals with B-CII. On the day of reimmunization, mice were symptom free, and were randomly assigned to C5 blocker treatment or control treatment groups. Each mouse was treated with either the C5 blocker (anti-mouse C5 mAb, BB5.1) or a control treatment (anti-human C8 mAb, 135.8) at 750μg per mouse ip twice

weekly. The animals were treated for four weeks, at which time treatment was discontinued. The results of this study are shown in Figures 4 and 5.

Administration the C5 blocker completely prevented the development of CIJI (0/8). All mice in the C5 blocker treated group exhibited no signs of clinical disease during the period of treatment (and for up to two months after discontinuing the C5 blocker therapy in the two animals followed for that long). In contrast, 90% of the control treated animals (9/10) developed JI by 4-6 weeks after the first B-CII immunization. The percent incidence of JI observed in the control treated and C5 blocker treated animals after 4-6 weeks is plotted in Figure 5a. (Note that the value for the C5 blocker treated group in this figure is actually 0%, but a bar indicating 1% has been plotted in order to indicate that the data for this set of animals was obtained and is presented.) Peak inflammation levels were observed around 5 weeks after the initial collagen immunization. As shown in Figure 5b, 80% to 90% of the serum hemolytic activity was depleted in the C5 blocker treated group, while the serum hemolytic activity remained normal in the control treated group.

As shown in Figure 4, histological examination of affected joints from control mice revealed extensive mononuclear cell as well as polymorphonuclear cell infiltration, thickening of the synovial membrane and bone erosion by the expanding synovial pannus (Figure 4b). In contrast, there were no signs of inflammatory processes observed in the majority of joints studied from the C5 blocker treated mice. A few joints from these C5 blocker treated mice showed some subclinical thickening of the synovial membrane, but this alteration was not accompanied by any visible bone erosion or inflammatory cell infiltration (Figure 4c). Interestingly, immunofluorescence staining showed antibody deposition along cartilage surfaces and C3 activation at synovial

membranes in the joints of both the control treated and the C5 blocker treated animals.

EXAMPLE 3

Effect of C5 Blocker Treatment on the Humoral and Cellular Immune Responses to Immunization with Collagen

Responses of both the humoral and cellular immune systems are activated after immunization of DBA/1LacJ mice with bovine Collagen II. Anti B-CII titers increase, and the serum IgG anti B-CII titers in C5 blocker treated mice are equivalent to those of control treated mice when tested at 14, 28 and 42 days after the initial B-CII immunization (Figure 6a). Anti B-CII antibody titers from both control and anti-C5 mAb treated mice rise significantly after the B-CII reimmunization and remain at the resulting plateau for an extended period of time.

In order to study T cell responses, lymph node cells (LNCs) from C5 blocker treated mice and control treated mice were cultured with either B-CII, B-CI, C-CII, or culture medium only. LNCs from either C5 blocker treated mice or control treated mice responded specifically and equally to B-CII regardless of the treatment the animals received concurrently with B-CII reimmunization. C-CII, which shares many conserved regions of homology with B-CII also elicited a moderate T cell response when cultured with LNCs from C5 blocker treated mice or from control treated mice. In contrast, LNCs from age matched non-immunized mice responded poorly to all of the tested collagens (Figure 6b).

The data obtained in these experiments and those of Examples 1 and 2 clearly demonstrate that in vivo administration of a C5 blocker prevents the development and progression of CIJI and that this treatment does not interfere with the humoral and cellular immune responses seen after immunizing mice with bovine type II collagen. Both collagen-specific T cell responses and anti-CII antibody titers were comparable in both the C5 blocker

treated mice and the control treated B-CII reimmunized mice.

EXAMPLE 4

C5 Blocker Inhibition of Complement Activity

The effects of a C5 blocker on complement activation were evaluated using a closed-loop cardio-pulmonary bypass (CPB) model for the extracorporeal circulation of human blood. As discussed fully in copending U.S. patent application Serial No. 08/217,391, filed March 23, 1994, extracorporeal circulation of human blood causes activation of complement in the blood.

The C5 blocker was a monoclonal antibody raised in mice against purified human C5 protein (Wurzner, et al., Complement Inflamm 8:328-340, 1991; mAb N19-8) that was propagated, recovered and purified as an IgG fraction from mouse ascites fluid (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Current Protocols In Immunology, John Wiley & Sons, New York, 1992).

To carry out these experiments, 300 ml of whole human blood was drawn from a healthy human donor and additionally a 1 ml sample was removed as a control sample for later analysis. The blood was diluted to 600 ml by the addition of Ringer's lactate solution containing 10U/ml heparin. The C5 blocker (30 mg in sterile PBS) was added to the diluted blood to a final concentration of 50 μg/ml. In a control experiment, an equal volume of sterile PBS was added to the diluted blood. The blood was then used to prime the extracorporeal circuit of a COBE CML EXCEL membrane oxygenator CPB machine (Cobe BCT, Inc., Lakewood, CO) and the circuit was started. The circuit was cooled to 28°C and circulated for 60 minutes. The circuit was then warmed to 37°C and circulated for an additional 30 minutes. The experiment was then terminated. Samples were taken at several time points and evaluated for complement activity (Figure 7).

At each time point an aliquot of white blood was taken, divided into 3 samples and A) diluted 1:1 in 2% paraformaldehyde in PBS to evaluate platelet and blood cell activation parameters as discussed in the above-referenced U.S. Patent Application Serial No. 08/217,391; B) centrifuged to remove all cells and plasma diluted 1:1 in Quidel sample preservation solution (Quidel Corporation, San Diego, CA) and stored at -80°C, following which these frozen diluted plasma samples were thawed and used to evaluate C3a and C5b-9 generation (Examples 5 and 6, respectively), and C) centrifuged to remove all cells and undiluted plasma stored at -80°C, following which these frozen plasma samples were thawed and hemolytic assays were performed as described above.

As can be seen in Figure 7, addition of the C5 blocker to the extracorporeal circuit resulted in a 95% reduction of the cell-lysing ability of complement in the plasma. The complement activity remained inhibited throughout the course (90 minutes) of the experiment.

EXAMPLE 5

Generation of C3a in the Presence of a C5 Blocker

The fresh frozen plasma samples that had previously been diluted in Quidel sample preservation solution following CPB circulation (see Example 4) were assayed for the presence of the complement split product C3a by using the Quidel C3a EIA kit (Quidel Corporation, San Diego, CA). These measurements were carried out according to the manufacturer's specifications. C3a released is expressed in ng/well as determined by comparison to a standard curve generated from samples containing known amounts of human C3a.

As seen in Figure 8, addition of the C5 blocker had no effect on the production of C3a during the CPB experiment. C3a generation was dramatically increased during the final 30 min. of the experiment and correlates with sample warming.

EXAMPLE 6

Prevention of the Generation of C5b-9 by a C5 Blocker

Fresh frozen plasma samples that had been previously diluted in Quidel sample preservation solution following CPB circulation (see Example 4) were assayed for the presence of the terminal human complement complex C5b-9 using the Quidel C5b-9 kit (Quidel Corporation, San Diego, CA). The amount of soluble C5b-9 (sC5b-9) in each sample was determined using the manufacturers specifications and is expressed in arbitrary absorbance units (AU).

As can be seen in Figure 9, the C5 blocker completely inhibited C5b-9 generation during extracorporeal circulation so that sC5b-9 levels during the full course of the run were equivalent to control (t_0) time points. The results of this experiment and those of Examples 4 and 5 show that the addition of a C5 blocker to human blood undergoing extracorporeal circulation effectively inhibits both complement hemolytic activity (Figure 7) and C5b-9 generation (Figure 9), but not C3a generation (Figure 8).

Example 7

Pharmacokinetics of mAb C5 Blockers

The in vivo duration of action of mAb BB5.1, and a Fab' fragment of mAb BB5.1 (prepared by standard methods) was determined in normal female BALB/cByJ mice (averaging approximately 20 gms each) which were obtained from the Jackson Laboratory, Bar Harbor, ME. The mice were given a single intravenous injection (at 35 mg/kg body weight) of the mAb or the Fab' fragment of the mAb (or an equal volume of PBS as a control). Blood samples were collected from the retroorbital plexus at 1, 4, 24, 96, and 144 hours after administration of PBS; 4, 16, and 24 hours after administration of the Fab' fragment of mAb BB5.1; and 4, 24, 48, 72, 96, and 144 hours after administration of intact mAb BB5.1.

Fig. 10a shows the time course of inhibition of the cell-lysing ability of complement in mouse blood (determined by testing serum obtained from the blood and diluted to 2.5% in hemolytic assays, as described above) after the in vivo administration of the intact mAb, the Fab' fragment, or the PBS. As shown in the figure, the intact mAb almost completely inhibited the hemolytic activity of the blood throughout the 6 day test period. The Fab', however, had a half-life of approximately 24 hours.

In addition to the above experiments, at the end of the 6 day testing period all of the mice were sacrificed. Kidneys, lungs, and livers were harvested and examined by gross inspection, as well as by microscopic examination of stained sections. All of the organs of the C5 blocker treated animals appeared the same as those taken from the PBS control treated animals. The overall appearance of these test and control mice was also indistinguishable prior to necropsy.

An anti-human C5 mAb was also tested for pharmacokinetic properties in circulating human blood as described above in Example 4. As described therein, the hemolysis-inhibiting effects of this C5 blocker were assayed over a 90 minute period of circulation. The results of these assays are charted in Figure 10b, and show that the C5 blocker essentially completely inhibited the cell lysing ability of the human blood during the entire 90 minute period of circulation.

The results of these experiments demonstrate that these C5 blockers will survive in the bloodstream for a substantial period of time, thus making periodic administration practical.

EXAMPLE 8

Preparation of a C5 Blocker

A C5 blocker mAb suitable for use in the practice of the present invention was prepared as follows.

Balb/c mice were immunized three times by intraperitoneal injection with human C5 protein (Quidel Corporation, San Diego, CA, Catalog #A403). The first injection contained 100µg of C5 protein in a complete Freund's adjuvant emulsion, the second immunization contained 100µg of C5 protein in an incomplete Freund's adjuvant emulsion, and the third immunization was 100µg of protein in PBS. The mice were injected at roughly 2 month intervals.

Fusions of splenocytes to myeloma cells to generate hybridomas were performed essentially as described in Current Protocols in Immunology (John Wiley & Sons, New York, 1992, pages 2.5.1 to 2.5.17). One day prior to fusion the mice were boosted IV with 100µg of C5 protein. On the day of fusion, the immunized mice were sacrificed and spleens was harvested. SP2/0-AG14 myeloma cells (ATCC CRL#1581) were used as the fusion partner. SP2/0-AG14 cultures were split on the day before the fusion to induce active cell division. A ratio of 1:10 (myeloma cells:splenocytes) was used in the fusions.

The cells were fused using PEG 1450 in PBS without calcium (Sigma Chemical Company, St. Louis, MO, Catalog No. P-7181) and plated at 1-2.5 x 10^5 cells per well. Selection in EX-CELL^{EX} 300 medium (JRH Biosciences, Lexena, KS, Catalog No. 14337-78P) supplemented with 10% heat inactivated fetal bovine serum (FBS); glutamine, penicillin and streptomycin (GPS); and HAT (Sigma Chemical Company, St. Louis, MO, Catalog No. H-0262) was started the following day. The fusions were then fed every other day with fresh FBS, GPS, and HAT supplemented medium. Cell death could be seen as early as 2 days and viable cell clusters could be seen as early as 5 days after initiating selection. After two weeks of selection in HAT, surviving hybridomas chosen for further study were transferred to EX-CELL 300 medium supplemented with FBS, GPS, and HAT (Sigma Chemical Company, St. Louis, MO, Catalog No. H-0137) for 1 week and then cultured in

EX-CELL 300 medium supplemented with FBS and GPS.

Hybridomas were screened for reactivity to C5 and inhibition of complement-mediated hemolysis 10-14 days after fusion, and were carried at least until the screening results were analyzed. The screen for inhibition of hemolysis was the chicken erythrocyte lysis assay described above. The screen for C5 reactivity was an ELISA, which was carried out using the following protocol.

A 50 µL aliquot of a 2µg/ml solution of C5 (Quidel Corporation, San Diego, CA) in sodium carbonate/bicarbonate buffer, pH 9.5, was incubated overnight at 4°C in each test well of a 96 well plate (Nunc-Immuno™ F96 Polysorp™, A/S Nunc, Roskilde, Denmark). The wells were then subjected to a wash step. (Each wash step consisted of three washes with TBST.) Next, test wells were blocked with 200 µL of blocking solution, 1% BSA in TBS (BSA/TBS), for 1 hour at 37°C. After an additional wash step, a 50µL aliquot of hybridoma supernatant was incubated in each test well for 1 hour at 37°C with a subsequent wash step. As a secondary (detection) antibody, 50µL of a 1:2000 dilution of horseradish peroxidase (HRP) conjugated goat anti-mouse IgG in BSA/TBS, was incubated in each test well for 1 hour at 37°C, followed by a wash step. Following the manufacturer's procedures, 10 mg of O-phenylenediamine (Sigma Chemical Company, St. Louis, MO, Catalog No. P-8287) was dissolved in 25 mLs of phosphate-citrate buffer (Sigma Chemical Company, St. Louis, MO, Catalog No. P-4922), and 50 µL of this substrate solution was added to each well to allow detection of peroxidase activity. Finally, to stop the peroxidase detection reaction, a 50µL aliquot of 3N hydrochloric acid was added to each well. The presence of antibodies reactive with C5 in the hybridoma supernatants was read out by a spectrophotometric OD determination at 490 nm.

The supernatant from a hybridoma designated as 5G1.1 tested positive by ELISA and substantially reduced the cell-lysing ability of complement present in normal human blood in the chicken erythrocyte hemolysis assay. Further analyses revealed that the 5G1.1 antibody reduces the cell-lysing ability of complement present in normal human blood so efficiently that, even when present at roughly one-half the molar concentration of human C5 in the hemolytic assay, it can almost completely neutralize serum hemolytic activity.

Hybridoma 5G1.1 was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland, 20852, United States of America, on April 27, 1994, and has been assigned the designation HB-11625. This deposit was made under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (1977).

Although preferred and other embodiments of the invention have been described herein, further embodiments may be perceived by those skilled in the art without departing from the scope of the invention as defined by the following claims.

REFERENCES

Abbink et al., 1992. Annals Rheumatic Dis 51, pp. 1123-1128.

Andersson and Holmdahl, 1990. Eur J Immunol 20, pp. 1061-1066.

Andersson et al., 1991. Immunology 73, pp. 191-196.

Andersson et al., 1992. Immunogenetics 35, pp. 71-72.

Arnett, 1992. Cecil Textbook of Medicine, Wyngaarden et al. (editors). W.B. Saunders Company, Philadelphia, Chapter 258, pp. 1508-1515.

Auda et al., 1990. Rheumatol Int 10, pp. 185-189.

Banerjee et al., 1988A. J Immunol 141, pp. 1150-1154.

Banerjee et al., 1988B. J Exp Med 167, pp. 832-839.

Banerjee et al., 1989. J Immunol 142, pp. 2237-2243.

Boissier et al., 1987. Annals Rheumatic Dis 46, pp. 691-700.

Brahn and Trentham, 1989. Cell Immunol 118, pp. 491-503.

Brodeur et al., 1991. Arthr Rheumat 34(12), pp. 1531-1537.

Cannon et al., 1990. Agents and Actions 29, pp. 315-323.

Cash and Klippel, 1994. New England J Med 330, pp. 1368-1375.

Chiocchia et al., 1990. J Immunol 145, pp. 519-525.

Chiocchia et al., 1991. Eur J Immunol 21, pp. 2899-2905.

Clackson et al., 1991. Nature 352, pp. 624-628.

Coligan et al. (eds.), 1992. Current Protocols In Immunology, John Wiley & Sons, New York.

Corvetta et al., 1992. Clinic Exp Rheumat 10, pp. 433-438.

David, 1992. Immunogenetics 35, pp. 69-70.

De Clerck et al., 1989. Clinic Exp Rheumat 7, pp. 485-492.

Drug Evaluations. Annual 1991. American Medical Association, 1990.

Durie et al., 1993. Science 261, pp. 1328-1330.

Elliot et al., 1993. Arthr Rheumat 36(12), pp. 1681-1690.

Fava et al., 1993. Clin Exp Immunol 94, pp. 261-266.

Feldmann et al., 1990. Annals Rheumat Dis 49(1), pp. 480-486.

Feldmann et al., 1991. Immunol Review 119, pp. 105-123.

Firestein et al., 1991. Arthr Rheumat 34(9), pp. 1094-1105.

Fong et al., 1994. Clin Exp Rheumat 12(1), pp. 55-58.

Frei et al., 1987. Mol Cell Probes 1, pp. 141-149.

Fujimori et al., 1993. Agents and Actions 39, pp. 42-48.

Gilman et al. (eds.), 1990. Goodman and Gilman's The Pharmacological Basis of Therapeutics 18th Ed. Pergamon Press, Inc., New York.

Goldschmidt et al., 1990. Immunol 69, pp. 508-514.

Goldschmidt and Holmdahl, 1991. Eur J Immunol 21, pp. 1327-1330.

Griswold et al., 1988. Arthrit Rheumat 31(11), pp. 1406-1412.

Haber, 1992. Immunol Rev 130, pp. 189-212.

Haqqi et al., 1989. Immunogenet 29, pp. 180-185.

Harigai et al., 1993. Clinic Immunol Immunopathol 69(1), pp. 83-91.

Harlow and Lane, 1988. Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York.

Heinz et al., 1989. Molecul Immunol 26(2), pp. 163-169.

Holmdahl et al., 1985. Scand J Immunol 22, pp. 295-306.

Holmdahl et al., 1986. Arthrit Rheumat 29(1), pp. 106-113.

Holmdahl et al., 1989. Clin Exp Rheumat 7(S-3), pp. 51-55.

Holmdahl et al., 1990. Scand J Immunol 31, pp. 147-157.

Hom et al., 1988. Eur J Immunol 18, pp. 881-888.

Hom et al., 1991. Agents and Actions 33, pp. 300-309.

Hom et al., 1992. Clinic Immunol Immunopath 62(1), pp. 56-65.

Hom et al., 1993. Immunological Investigations 22(4), pp. 257-265.

Hong et al., 1979. J Immunol 122(6), pp. 2418-2423.

Inoue et al., 1993. Agents and Actions 39, pp. 187-194.

Jasin, 1989. Sem Arthrit Rheumat 18(4), pp. 86-90.

Jose et al., 1990. Annals Rheumat Dis 49, pp. 747-752.

Kabat and Mayer, 1961. Experimental Immunochemistry, 2nd Ed. Charles C. Thomas, Springfield, Illinois, pp. 135-139.

Kahle et al., 1992. Annals Rheumat Dis 51(6), pp. 731-734.

Kakimoto et al., 1988. J Immunol 140(1), pp. 78-83.

Kakimoto et al., 1992. Cellular Immunology 142, pp. 326-337.

Kleinau et al., 1989. Clin Exp Immunol 78, pp. 138-142.

Koch et al., 1994. J Clin Invest 94, pp. 1012-1018.

Liddell and Cryer, 1991. A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England.

Lipsky, 1994. Harrison's Principles of Internal Medicine, 13th Ed, Isselbacher et al. (eds). McGraw-Hill, Inc., New York, Chapter 285, pp. 1648-1655.

Maeurer et al., 1992. Immunobiol 185, pp. 103-120.

Matsubara et al., 1991. Am J Pathol 138(5), pp. 1279-1291.

McCarty and Koopman, 1993. Arthritis and Allied Conditions, 12th Ed. Lea and Febiger, Philadelphia.

Moffat et al., 1989. Clin Exp Immunol 78, pp. 54-60.

Mollnes et al., 1986. Arthr Rheumat 29(6), pp. 715-721.

Mollnes et al., 1988. Scand J Immunol 28, pp. 307-312.

Montz et al., 1990. Cellular Immunol 127, pp. 337-351.

Mori et al., 1992. J Exp Med 176, pp. 381-388.

Morgan et al., 1981. Arthrit Rheumat 24(11), pp. 1356-1362.

Morgan et al., 1988. Clin Exp Immunol 73, pp. 473-478.

Morrison, 1992. Annu Rev Immunol 10, pp. 239-265.

Moxley and Ruddy, 1985. Arthr Rheumat 28(10), pp. 1089-1095.

Muller-Eberhard, 1988. Ann Rev Biochem 57, pp. 321-347.

Myers et al., 1989A. J Immunol 143(12), pp. 3976-3980.

Myers et al., 1989B. J Exp Med 170, pp. 1999-2010.

Myers et al., 1993. J Immunol 150(10), pp. 4652-4658.

Nagler-Anderson et al., 1986. Proc Natl Acad Sci, USA 83, pp. 7443-7446.

Nakajima et al., 1993. Clin Exp Immunol 92, pp. 328-335.

Nishikaku and Koga, 1993. Immunopharmacology 25, pp. 65-74.

Oleesky et al., 1991. Clin Exp Immunol 84, pp. 250-255.

Olmez et al., 1991. Scand J Rheumatol 20, pp. 183-189.

Olsen et al., 1991. Arthr Rheumat 34(2), pp. 187-191.

Osman et al., 1993. J Exp Med 177, pp. 387-395.

Peake et al., 1989. Clin Exp Immunol 78, pp. 49-53.

Peterman et al., 1993. J Immunol 151(11), pp. 6546-6558.

Physicians' Desk Reference 47th Ed., 1993. Medical Economics Co., Inc., Montvale, NJ.

Piguet et al., 1992. Immunol 77, pp. 510-514.

Reichamnn et al., 1988. Nature 332, pp. 323-327.

Reife et al., 1991. Arthr Rheumat 34, pp. 776-781.

Remington's Pharmaceutical Sciences 17th Ed., 1985. Mack Publishing Company, Philadelphia, PA.

Rodrigues et al., 1993. J Immunol 151, pp. 6954-6961.

Roitt et al., 1988. Essential Immunology, 6th Ed. Backwell Scientific Publications, Oxford, England.

Saura et al., 1992. Rheumat 12, pp. 141-146.

Seki et al., 1988. J Immunol 140(5), pp. 1477-1484.

Seki et al., 1992. J Immunol 148(10), pp. 3093-3099.

Shingu et al., 1994. British J Rheumat 33, pp. 299-301.

Smith et al., 1990. Int J Immunopharmac 12(2), pp. 165-173.

Spannaus-Martin et al., 1990. Am J Path 137(2), PP. 331-339.

Spinella and Stuart, 1992. Immunogenetics 35, pp. 73-74.

Spinella et al., 1991. Immunogenetics 34, pp. 23-27.

Terato et al., 1992. J Immunol 148(7), pp. 2103-2108.

The United States Pharmacopeia 22nd Ed., 1989. Mack Printing Co., Easton, PA.

Thompson et al., 1988. Clin Exp Immunol 72, pp. 20-25.

Thorbecke et al., 1992. Proc Natl Acad Sci. USA 89, pp. 7375-7379.

Trentham et al., 1977. J Exp Med 146, pp. 857-868.

Trentham et al., 1993. Science 261, pp. 1727-1730.

van Lent et al., 1992. Am J Path 140, pp. 1451-1461.

Ward and Zvaifler, 1971. J Clinical Invest 50, pp. 606-616.

Ward, 1975. Annals NY Acad Sci 256, pp. 169-176.

Watson and Townes, 1985. J Exp Med 162, pp. 1878-1891.

Watson et al., 1987. Arthrit Rheumat 30(4), pp. 460-465.

Williams et al., 1992A. Clin Exp Immunol 88, pp. 455-460.

Williams et al., 1992B. Proc Natl Acad Sci. USA 89, pp. 9784-9788.

Williams et al., 1994. Proc Natl Acad Sci, USA 91, pp. 2762-2766.

Winter and Milstein, 1991. Nature 349, pp. 293-299.

Wolos et al., 1993. J Immunol 151(1), pp. 526-534.

Wurzner et al., 1991. Complement Inflamm 8, pp. 328-340.

Yoo et al., 1988. J Exp Med 168, pp. 777-782.

Zvaifler, 1968. Univ Michigan Med Center J, pp. 234-237.

Zvaifler, 1969A. Annals NY Acad Sci 168(1), pp. 146-160.

Zvaifler, 1969B. J Clinical Invest 48, pp. 1532-1542.

Zvaifler, 1974. Arthr Rheumat 17(3), pp. 297-305.

TABLE 1

		NUMBER OF LIMBS AFFECTED PER GROUP*			
Treatment	n	Day 0	Day 10	% Change	% Hemolytic Activity
Control	4	4 (1.0)	9 (2.3)	+125.0	95.6 ± 3.8
C5 Blocker	6	8 (1.3)	7 (1.2)	- 12.5	13.9 ± 4.7

* Numbers in parenthesis represent the average number of affected joints per mouse.

TABLE 2

Mouse (treatment)	NUMBER OF LIMBS AFFECTED PER MOUSE			
	Day 0	Day 10	% Change	% Hemolytic Activity
#8 (control)	1 (RL)	2 (RL & RR)	+100	91.2
#2 (C5 blocker)	1 (FL)	1 (FL)*	0	22.4
#6 (control)	1 (RR)	2 (RR & RL)	+100	103.2
#5 (C5 blocker)	1 (RR)	1 (RR)	0	6.0
#1 (control)	1 (FL)	2 (FL & FR)	+100	92.4
#4 (C5 blocker)	1 (RL)	2 (FL & RL)	+100	9.2
#9 (control)†	1 (RL)	2 (RR & RL)	+100	not tested
#3 (C5 blocker)†	2 (FL & RR)	1 (FL)	-100	0.4
#7 (C5 blocker)§	1 (FR)	1 (FR)	0	13.6
#10 (C5 blocker)§	2 (RL & RR)	1 (RR)**	-100	32.0

* barely detectable inflammation

** only 1 toe

† data represent only 8 days for mouse #9 and #3

§ mouse #7 and #10 were not provided with matched controls

2198706

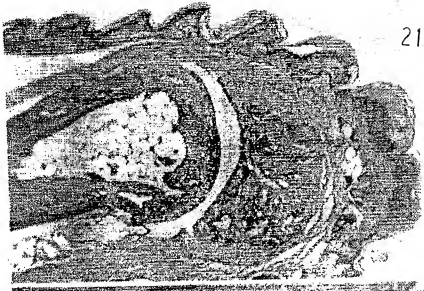

Fig. 1a

Fig. 1b

Fig. 1c

2198706

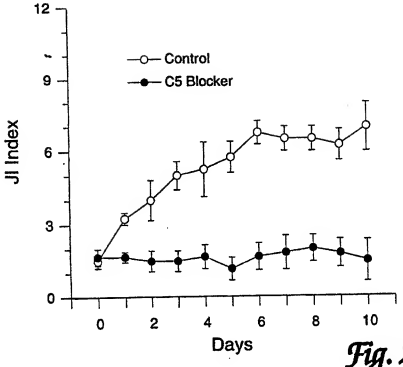

Fig. 2a

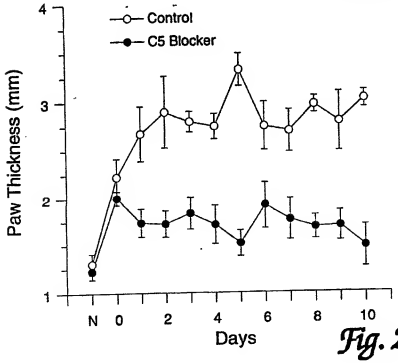

Fig. 2b

2198706

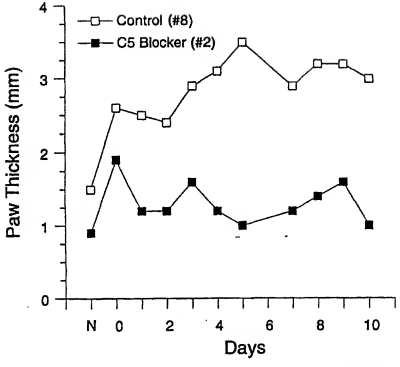

Fig. 3a

2198706

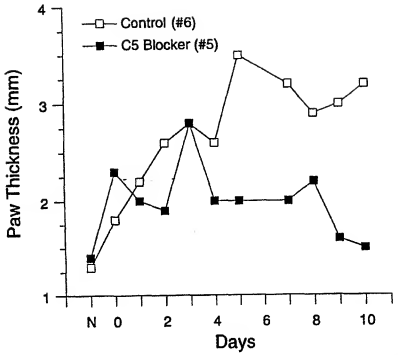

Fig. 3b

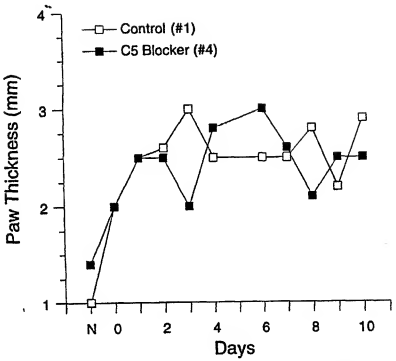

Fig. 3c

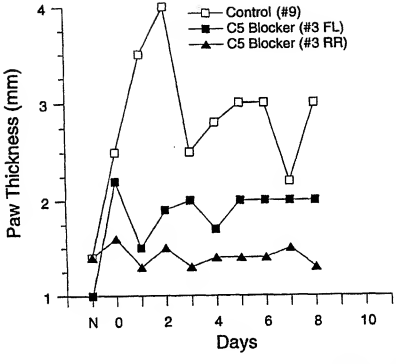
Control (#9)
C5 Blocker (#3 FL)
C5 Blocker (#3 RR)
Paw Thickness (mm)
4
3
2
1
N
0
2
4
6
8
10
Days

Fig. 3d

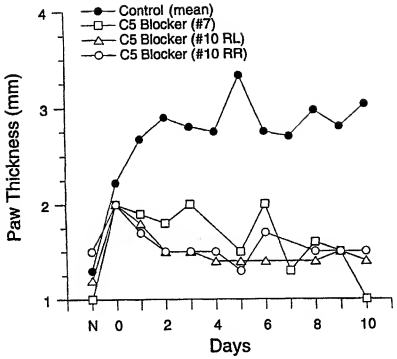
Control (mean)
C5 Blocker (#7)
C5 Blocker (#10 RL)
C5 Blocker (#10 RR)
Paw Thickness (mm)
4
3
2
1
N
0
2
4
6
8
10
Days

Fig. 3e

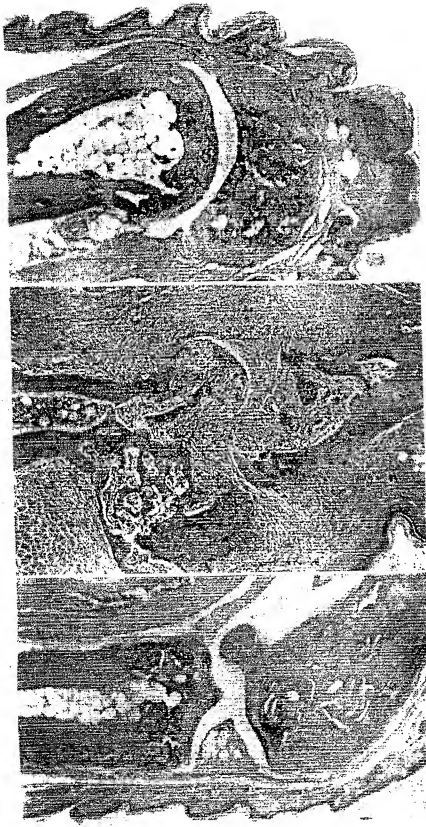

Fig. 4a

Fig. 4b

Fig. 4c

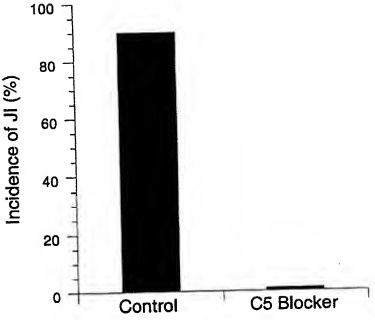
Incidence of JI (%)
100
80
60
40
20
0
Control
C5 Blocker

Fig. 5a

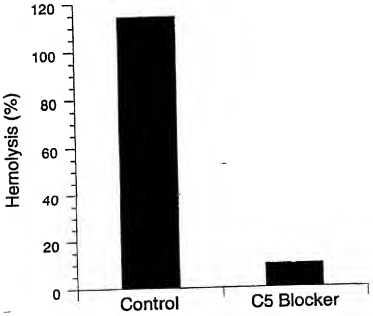
Hemolysis (%)
120
100
80
60
40
20
0
Control
C5 Blocker

Fig. 5b

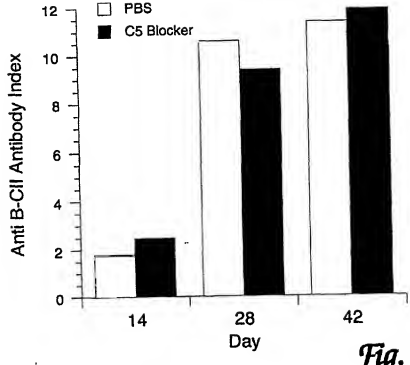
PBS
C5 Blocker
Anti B-CII Antibody Index
12
10
8
6
4
2
0
14
28
42
Day

Fig. 6a

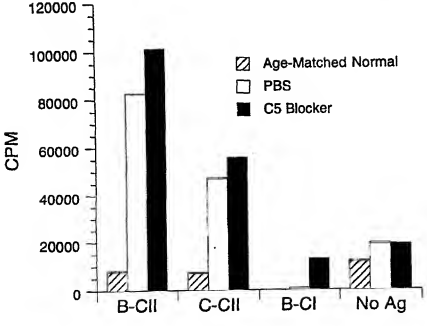
120000
100000
80000
60000
40000
20000
0
CPM
Age-Matched Normal
PBS
C5 Blocker
B-CII
C-CII
B-CI
No Ag

Fig. 6b

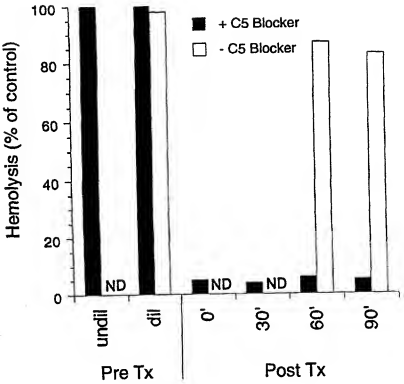
100
80
60
40
20
0
Hemolysis (% of control)
+ C5 Blocker
- C5 Blocker
ND
ND
ND
undil
dil
0'
30'
60'
90'
Pre Tx
Post Tx

Fig. 7

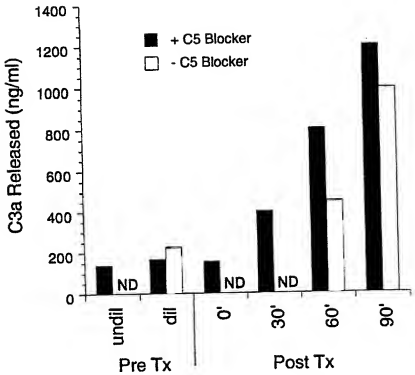
1400
1200
1000
800
600
400
200
0
C3a Released (ng/ml)
+ C5 Blocker
- C5 Blocker
ND
ND
ND
undil
dil
0'
30'
60'
90'
Pre Tx
Post Tx

Fig. 8

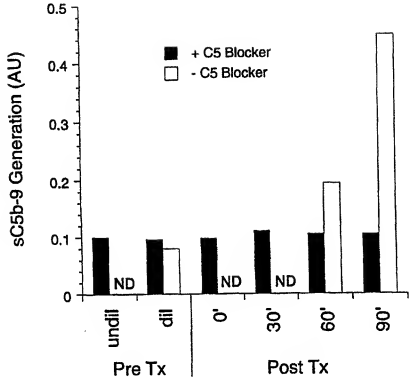
sC5b-9 Generation (AU)
0.5
0.4
0.3
0.2
0.1
0
+ C5 Blocker
- C5 Blocker
ND
ND
ND
undil
dil
0'
30'
60'
90'
Pre Tx
Post Tx

Fig. 9

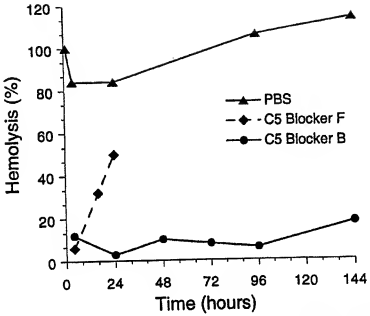

Fig. 10a

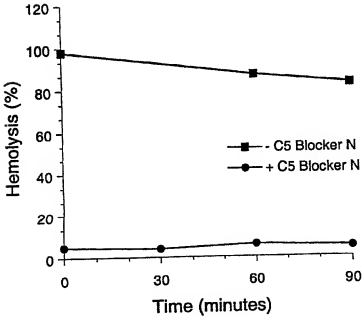

Fig. 10b